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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/749,437	12/31/2003	Kwen-Jen Chang	4080-130	8959

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EXAMINER	
KWON, BRIAN YONG S	
ART UNIT	PAPER NUMBER
1614	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/30/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/749,437	CHANG ET AL.	
	Examiner	Art Unit	
	Brian S. Kwon	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *1-7,9-13,15-19,29 and 30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8,14,20-28 and 31-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. Acknowledgement is made of applicant's filing of amendment on 02/16/07. Applicant's arguments have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of actions being applied to the instant application.

2. Claims 8, 14, 20-28 and 31-40 are currently pending for prosecution on the merits of the case.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 8, 14, 20-23, 27-28, 33-34 and 38-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chang et al. (US 7030124 B2) in view of Schultz et al. (US 6103722).

Chang teaches diarylpieprazine compounds of formula (1) including compounds (i), (vii), (viii), (xii) and (xiii) or pharmaceutically acceptable ester (including carboxylic acid esters of the hydroxyl group in the compounds of formula (1)) or salt thereof that is useful as delta opioid receptor agonist (column 1, lines 17-22 and column 3, line 50 thru column 8, line 65), wherein said compound is formulated in various dosage formulation including oral, rectal, topical, sub-lingual, mucosal, nasal, ophthalmic, subcutaneous, intramuscular, intravenous, transdermal, spinal, intrathecal, intra-articular, intra-arterial, sub-arachnoid, bronchial, lymphatic and intra-uterine forms (column 9, lines 6-12), and wherein said compound is administered in dosage range of 10 micrograms to 100 milligrams per kg body weight per day, preferably in the range of 50 microgram to 75 mg/kg per day and most preferably in the range of 100 microgram to 50 mg/kg per day over two, three, four, five, six or more sub-doses administered at appropriate intervals throughout the day (column 25, line 53 thru column 2, line 5) for the treatment of depression. Chang discloses that Ar^2 can be 6-member carbocyclic with carbon atom thereof a substitute X, wherein X is selected from the group consisting of hydrogen, halogen, hydroxy and alkoxy (column 3, lines 19-42; column 22, lines 34-37).

Schultz teaches use of delta opioid receptor agonist including diarylmethylpiperazine compound such as BW373U86 and SNC80 as a cardioprotective agent for reducing ischemic damage or ischemia and reperfusion injury (e.g., angina pectoris, myocardial infarction and restenosis) or blocking ischemic preconditioning in mammal including human (abstract; column 1, lines 20-25; column 3, line 61 thru column 4, line 37; column 7, lines 8-12; Figures) wherein said delta opioid receptor agonist is administered prior, during or after the ischemic event or ischemia or surgery (column 12, lines 53-57; Example 1 and 2), and wherein said compound is administered in various dosage forms including oral or injection per day, either at once or spread over several times (column 12, lines 58-67).

The teaching of Chang differs from the claimed invention in (i) the selection of the specific species, namely 4-{(2R,5S)-4-[(R)-(4-diethylcarbamoylphenyl)(3-hydroxyphenyl)methyl]-2,5-dimethyl-1-piperazinylmethyl]benzoic acid and the administration of said compound to a patient having or at risk of having ischemia or ischemic event to reduce ischemic damage to the human heart, block ischemic preconditioning (claims 8, 14, 20-28 and 31-40), and (ii) the administration of said compound in "multiple times currently with the onset of an ischemic event" (claim 20) and "after the onset of an ischemic event" (claim 23).

To incorporate such teaching into the teaching Chang, would have been obvious in view of Schultz who teaches the utility of using delta opioid receptor agonist such diarylmethylpiperazine compounds as a cardioprotective agent for reducing ischemic damage or ischemia and reperfusion injury to human or human heart, or blocking ischemic preconditioning and the administration of delta opioids in various dosage forms including oral and dosage administration regimen (e.g., per day, at once or spread over several times).

It would have been obvious to one having ordinary skill in the art at the time of the invention to select any of the species of the genus taught by the reference, including those of the claims, because an ordinary artisan would have the reasonable expectation that any of the species of the genus would have similar properties, thus, the same use as the genus as a whole.

Furthermore, one having ordinary skill in the art would have expected as taught by Schultz that the drugs having diarylmethylpiperazine core structure compound having delta opioid receptor agonist is useful in the therapeutic treatment of ischemia, ischemic damage or blocking ischemic preconditioning.

With respect to the selection of the specific administration regimen (particularly prior, during or after the onset of an ischemic event) and dosage forms (particularly oral and other forms including parenteral, rectal, topical, ophthalmic, subcutaneous, intramuscular, intravenous, transdermal, etc...), those of ordinary skill in the art would have been readily determined dosages and concurrent administration regimens as determined by good medical practice and the clinical condition of the individual patient. Determination of the appropriate dosage or administration regimen for treatment involving each of the above mentioned formulations is routinely made by those of ordinary skill in the art and is within the ability of tasks routinely performed by them without undue experimentation, especially in light of the administration regimen and dosage information disclosed in the Chang and Schultz.

With respect to "non-analgesic diarylmethylpiperazine compound of the formula" (claims 14, 20-28",

Since such property or characteristic must be expected feature of said diarylmethylpiperazine within the prior art dosage range, the references in combination makes obvious the instant invention.

Thus, one would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same ingredients and share common utilities), and pertinent to the problem which applicant concerns about. MPEP 2141.01(a).

4. Claims 24-26, 31-32 and 35-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chang et al. (US 7030124 B2) in view of Schultz et al. (US 6103722), and further in view of Applicant's admission of the prior art (page 9, lines 5-7).

The modified teaching of Chang includes all that is recited in claims 24-26, 31-32 and 35-37 except the use of second agent (claims 24-26, 31-32 and 35-37), namely as nitrates, beta-adrenergic blockers, calcium channel antagonist, ACE inhibitors, non-peptide angiotensin II antagonist, Iib/IIIa antagonists, aspirin (claims 25 and 36) and arginine hydrochloride (claim 32) and the administration of the second compound contemporaneously with the diarylmethylpiperazine compound (claims 26 and 37).

Applicant's admission of the prior art teaches the use of nitrates, beta-adrenergic blockers, calcium channel antagonist, ACE inhibitors, non-peptide angiotensin II antagonist, Iib/IIIa antagonists and aspirin as known cardiac therapeutic agent.

Oeltegen is being supplied a supplemental reference to demonstrate the state of art knowledge in using arginine hydrochloride as a cardiac therapeutic agent (column 3, lines 65-67 and claim 8).

Above references in combination make clear that the diarylmethylpiperazine compound and the second agent (e.g., nitrates, beta-adrenergic blockers, calcium channel antagonist, ACE inhibitors, non-peptide angiotensin II antagonist, Iib/IIIa antagonists and aspirin and arginine) have been individually used for the treatment of ischemia or ischemic damage to heart. It is obvious to combine two compositions each of which is taught by prior art to be useful for same purpose; idea of combining them flows logically from their having been individually taught in the prior art. The combination of active ingredient with the same character is merely the additive effect of each individual component. *See In re Kerkhoven, 205 USPQ 1069 (CCPA 1980).*

With respect to the determination of the specific administration regimen, namely "administered contemporaneously with the diarylmethylpiperazine compound", those of ordinary skill in the art would have been readily determined concurrent administration regimens as determined by good medical practice and the clinical condition of the individual patient. Determination of the appropriate administration regimen for treatment involving each of the above mentioned formulations is routinely made by those of ordinary skill in the art and is within the ability of tasks routinely performed by them without undue experimentation, absence evidence to the contrary.

Response to Arguments

5. Applicant's arguments filed 02/16/2007 have been fully considered but they are not persuasive.

Applicant's argument in the response takes the position that Chang'124 fails to teach or suggest the carboxy-substituted benzyl functional group.

This argument is not found persuasive. Unlike the applicant's argument, Chang'124 makes obvious that preparation of the compound of the formula I where Ar2 is 6-member carbocyclic carbocyclic (e.g., phenyl) with hydroxy substitution or its ester (including carboxylic acid ester of the hydroxyl group) is within the skill of the artisan. See column 22, lines 34-36 and column 23, line 44.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). Particularly, Schultz'722 provides nexus between delta opioid receptor agonist and the treatment of ischemic damage or ischemia and reperfusion injury to human or human heart. Thus, one would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same ingredients and share common utilities), and pertinent to the problem which applicant concerns about. MPEP 2141.01(a).

Conclusion

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

7. No Claim is allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached on (571) 272-0718. The fax number for this Group is (571) 273-8300.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about PAIR system, see http://pair-direct.uspto.gov Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Brian Kwon
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